19

INVOLVEMENT OF EXTRAHYPOTHALAMIC CORTICOTROPIN-RELEASING FACTOR (CRF) IN DRUG DEPENDENCE PROCESSES. [1]F. Weiss, [2]E.M. Pich, [3]R. Richter. [1]The Scripps Research Institute, La Jolla, CA; [2]Glaxo Institute for Molecular Biology, Geneva, Switzerland; [3]Institute of Molecular Pharmacology, Berlin, Germany.

Recent research suggests a role for CRF neurons in the central nucleus of the amygdala (CeA) in the mediation of behavioral and emotional responses to stress. For example, stress-like autonomic and behavioral responses associated with CRF administration can be mimicked by electrical stimulation of the CeA. In contrast, lesions of the CeA attenuate conditioned fear responses and produce anticonflict effects. Similarly, the anxiogenic actions of exogenous CRF in behavioral tests of anxiety are effectively reversed by administration of the CRF antagonist α-helical CRF(4-41) into the CeA. A recent demonstration that intra-CeA injection of α-helical CRF(4-41) reverses anxiety induced by ethanol withdrawal suggested that the integrative role of CRF mechanisms in the CeA in the mediation of physiological and emotional responses to stress may extend to drug dependence processes. To examine this hypothesis, CRF release was monitored in the CeA of male Wistar rats by intracranial microdialysis under conditions thought to be relevant to the development or maintenance of drug dependence: (1) after repeated exposure to cocaine, and (2) during withdrawal from chronic ethanol. In Experiment 1, intermittent cocaine administration over a 10-day period (30 mg/kg/day), a procedure that is often associated with the induction of behavioral sensitization to cocaine, significantly enhanced the effects of both a cocaine challenge injection and depolarization by 4-aminopyridine on CRF release. These results suggest that augmentation of CRF release in the CeA may play a role in behavioral and neurochemical sensitization observed after repeated psychostimulant treatments as well as in the cross-sensitization between stress and psychostimulant drugs. In Experiment 2, a progressive increase in CRF release was noted during withdrawal from ethanol in rats that had been maintained on an ethanol liquid diet for 2-3 weeks. Peak elevations in CRF release reached approximately 470% of baseline levels and occurred 10-12 hours after the onset of withdrawal. The time course of the elevation in extraneuronal CRF corresponds to the time of appearance of anxiogenic effects in behavioral work providing support for the hypothesis that CRF neurons in the amygdala participate in the mediation of the aversive effects of ethanol withdrawal. Together, the results confirm a function for CRF in the CeA in the consequences of chronic cocaine and alcohol abuse.

Galanin

20

GALANIN RECEPTOR DIFFERENCES USING [^{125}I]GALANIN (HUMAN, PORCINE, OR FRAG 1-16) OR [^{125}I]GALANTIDE. D.C. Deecher.[1] New Lead Discovery, Abbott Laboratories, Abbott Park, IL, [1]Currently at Women's Health Research Institute, Wyeth Ayerst, Radnor, PA.

Galanin is a biologically active peptide reported to be important in a variety of physiological functions. However, the role of galanin is poorly understood due to lack of sufficient number of compounds that interact with galanin receptors. The purpose of this study was to identify binding differences between 4 radioligands that interact with the galanin receptor. Radioligand binding experiments were done using [^{125}I]galanin (human, porcine or Frag 1-16) or [^{125}I]galantide to discern any binding differences between these radioligands in the different tissues tested. Slowly reversible kinetics were noted for all radioligands used, therefore all equilibrium binding experiments were run at saturation. Scatchard analysis using these 4 radioligands showed differences in receptor number in both human hypothalamus and basal forebrain and RINm5f cells. Competition of galanin and galanin chimeric peptides for the radioligands discerned receptor differences based on rank order affinities between regions and tissues. Results of these experiments showed differences between labeling by radioligand as well as species and region differences of galanin receptors. In conclusion, based on radioligand binding experiments galanin receptor subtypes are evident.